Questionable Antipsychotic Prescribing Remains Common, Despite Serious Risks

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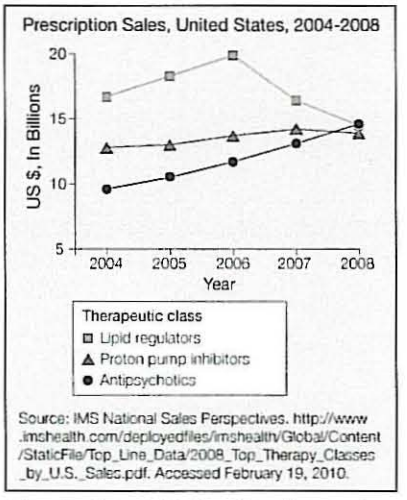
DESPITE THEIR ASSOCIATION WITH serious cardiac and metabolic risks, atypical antipsychotics are widely used off-label with few data to support their efficacy, according to recent studies probing use of this class of drugs in the United States. Furthermore, physicians often do not follow through on precautions to reduce these risks.

The studies provide new insights on physician prescribing behavior and the effect of warnings aimed at minimizing risks. The findings have raised new concerns about the public health impact and costs of widespread off-label antipsychotic use.

Antipsychotic drugs became the top-selling drug class in the United States in 2008, edging out lipid regulators and proton pump inhibitors, according to IMS Health, a company that gathers and analyzes data on pharmaceuticals. Sales of antipsychotic drugs in 2008 reached $14.6 billion, up from $9.6 billion in 2004. Antidepressants now rank fifth, with sales of $9.6 billion in 2008. This commercial success suggests that atypical antipsychotics were being used widely beyond indications approved by the US Food and Drug Administration (FDA), which until lately were limited to conditions such as schizophrenia and bipolar mania. The studies confirm this trend.

Researchers speculate that some of the enthusiasm for atypical antipsychotics may have been driven by a perception that these drugs were more effective and had fewer adverse effects than their predecessors. However, a growing body of evidence indicates these drugs are no more effective and are associated with serious risks of their own.

Since the period examined in many of the studies, the FDA has expanded some of the indications for these drugs. This, in turn, is likely to drive further



Source: IMS National Sales Perspectives. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/2008_Top_Therapy_Classes_by_U.S._Sales.pdf. Accessed February 19, 2010.

Sales of antipsychotic drugs have increased steadily since 2004, and now top sales for other popular drug classes such as lipid regulators and proton pump inhibitors.

increases in antipsychotic prescribing. For example, aripiprazole was approved for use as an adjunctive therapy for major depression in late 2007, as was quetiapine in December 2009.

SAFETY WARNINGS

The new findings suggest that warnings about the potential risks associated with use of atypical antipsychotics may have had limited or unintended effects.

In 2003, the FDA announced it would require makers of atypical antipsychotics to include warnings about the risks of hyperglycemia and diabetes, including death, in patients taking these drugs. Additionally, the revised labels noted that physicians should monitor glucose levels in patients with diabetes or with risk factors for the disease. The American Psychiatric Association and the American Diabetes Association also published a consensus statement outlining the risks and recommending glucose monitoring (http://care.diabetesjournals.org/content/27/2/596.full).

Yet a study that examined Medicaid records for 109 451 individuals who began taking atypical antipsychotics between 2002 and 2005 and 203 527 controls in California, Missouri, and Oregon found low levels of baseline glucose monitoring in patients taking the drugs and little boost in such monitoring after the warning (Morrato EH et al. *Arch Gen Psychiatry*. 2010;67[1]:17-24). The findings were consistent with studies that examined patients covered by private insurers, the authors noted. However, the authors did find evidence that the physicians were shifting away from atypical antipsychotics associated with the highest metabolic risks, and toward those that appeared to have lower risks.

Surveys suggest that while psychiatrists are aware of the warning and understand the importance of metabolic screening, other factors may be interfering, said Elaine H. Morrato, DrPH, MPH, of the Colorado School of Public Health, in Aurora. For example, patients may have limited access to testing, or may be receiving care from multiple sources. Furthermore, patients with disorders treated with antipsychotics may have psychosocial problems that make them less likely to follow through with recommended monitoring.

Morrato emphasized the importance of physicians conducting baseline and

routine follow-up screening when using these drugs. She also encouraged physicians to make sure that their patients understand why it is important to follow through with the screening.

In 2005, the FDA warned physicians that use of atypical antipsychotics to treat behavior problems in elderly patients increased the risk of death. While there is some evidence that rates of prescribing have decreased in this population, use for this indication remains common. One analysis looked at records from 2003 to 2008 in IMS Health's National Disease and Therapeutic Index, a nationally representative audit of office-based physicians' use of medications to treat patients. It found that before the warning was issued, physician prescribing of this class of medications was increasing 34% annually overall and rising 16% annually in patients with dementia (Dorsey ER et al. *Arch Intern Med.* 2010;170[1]: 96-103). After the advisory, overall use of atypical antipsychotics decreased 2%; use in elderly patients with dementia decreased 19%, although a substantial amount continued. One limitation of the study is that it captured only information about use in nursing home patients in the care of office-based physicians.

G. Caleb Alexander, MD, one of the studies' authors and an assistant professor of medicine at the University of Chicago, said that the study was not designed to assess whether the use of these drugs was appropriate. But he noted that the management of agitation in patients with dementia presents dilemmas for physicians and family members who may perceive a short-term benefit of using these drugs despite the risks.

"There are a limited number of pharmacologic options to treat the agitation that many patients with dementia have," he said. "This is partly why there is such an emphasis on trying to improve nonpharmacologic interventions, such as trying to optimize the environment the patient is in, maximize the patient's orientation and limit confusion, and otherwise comfort the patient and provide a setting where drug therapy can be avoided or minimized."

Alexander said that the results suggest a substantial change in the trajectory of second-generation antipsychotic prescribing, including unintended effects on prescribing for patients with indications other than dementia. He said more research is needed on the impact of such warnings and how they might be improved.

A second study, published simultaneously, looked specifically at nursing home residents and found continued high rates of prescribing in 2006, including variations in prescribing by facility (Chen Y et al. *Arch Intern Med.* 2010;170[1]:89-95). The study, which analyzed a nationwide sample of more than 16 000 nursing home residents, found that 4818 (29%) received at least one antipsychotic in 2006; of these, 1545 (32%) had no clinical indication cited. Additionally, patients were 1.37 times more likely to receive an antipsychotic if they lived in a facility with a high rate of prescribing than if they lived in a facility in which such prescribing was low.

Becky A. Briesacher, PhD, one of the studies' authors and an associate professor of medicine at the University of Massachusetts Medical School in Worcester, said the fact that studies including more recent data find greater declines in prescribing may mean there was a delayed reaction to the FDA warning. However, the finding that characteristics of facilities, not just patients, contribute to prescribing requires further probing. Briesacher explained that it is not clear what role might have been played by factors such as a lack of qualified staff or greater institutional acceptance of antipsychotic use.

More education, Briesacher said, could promote more informed use of these drugs. "One thing we need to do is make sure the risks are well understood by physicians, nursing staff, and families," she said. She also noted that in nursing homes with high rates of prescribing, patients were often given the drugs in their first week of residence, while facilities with lower rates waited longer. She explained that the first week in a new place may be a vulnerable time for patients, who may be disoriented or frightened. "Waiting until patients are more settled may help," she said.

WIDE OFF-LABEL USE

Other findings suggest that wide off-label prescribing continues and that in some cases physicians may not be aware that these applications are off-label.

An analysis of prescribing data from the Department of Veterans Affairs found that 60.2% of the 279 778 individuals who received at least one prescription for an antipsychotic medication in fiscal year 2007 had no record of a diagnosis for an FDA-approved indication (Leslie DL et al. *Psychiatr Serv.* 2010;60[9]:1175-1181). Rates of off-label antipsychotic use were highest among patients diagnosed with other psychoses (40.7%), major depression (20.5%), Alzheimer disease or other dementia-like illness (20%), and posttraumatic stress disorder (19.4%).

Douglas L. Leslie, PhD, professor of public health sciences and psychiatry at the Penn State College of Medicine in Hershey, Pa, said that physicians may be choosing to prescribe these drugs off-label—despite the limited evidence supporting their use—because they have heard anecdotal stories of benefit.

Leslie and colleagues also noted the tremendous costs of such off-label use. The dose typically used in schizophrenia patients costs $10 per day. Adjusting for the lower doses typically used for off-label applications, the researchers estimate that $4 billion to $5 billion of the $13.1 billion spent in the United States on antipsychotic drugs in 2007 may have been for off-label uses with little or no documented benefit.

"It's hard to justify, especially when we have good evidence-based treatments for mental disorders. The money would be better spent using those strategies," Leslie said.

One recent survey suggests that some physicians may not realize they are prescribing drugs off-label. The random mail survey of 599 primary care physicians and 600 psychiatrists (with an

adjusted response rate of 47%) between November 2007 and August 2008 asked physicians about 14 drug-indication pairs (Chen DT et al. *Pharmacoepidemiol Drug Saf.* 2009;18[11]: 1094-1100). It found that on average the physicians correctly identified the FDA approval status of half the drugs, though accuracy increased to 60% when the scientists looked only at drugs the physician reported prescribing frequently. Additionally, 42% of the physicians reported prescribing quetiapine for dementia with agitation, and 19% mistakenly believed the drug was approved for this indication.

Alexander, who was a member of the research team, suggested a number of possible reasons for this disconnect. To begin with, the evidence base for drugs is enormous and difficult for physicians to master. Moreover, with psychiatric drugs, which are frequently used off-label for evidence-based and non–evidence-based reasons, Alexander said, there may be greater room for clinical innovation, greater difficulty establishing the boundaries of evidence, and more shared mechanisms of disease.

"I think [antipsychotic drugs] have been widely overused," Alexander said. "Efforts are needed to educate physicians more regarding the evidence base, and prescribers need to have more scrutiny and restraint in using psychotropic therapies." □

Study Findings Offer Conflicting Views on Future Role of Carotid Artery Stenting

Mike Mitka

STENTING MAY SOON JOIN THE treatment arsenal available to patients needing correction of severe carotid artery stenosis to minimize stroke risk. Whether it should be available remains a question.

At the February meeting of the American Stroke Association in San Antonio, Tex, researchers presented data gathered from the United States and Canada showing that carotid artery stenting was basically as safe and effective in preventing stroke, myocardial infarction, or death as carotid endarterectomy, the gold standard for treating severe carotid artery stenosis. The findings come from the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). Additional funding was provided by Abbott Laboratories, maker of the stent used in the study.

But just a day before the CREST presentation, results were published from the International Carotid Stenting Study (ICSS), which compared endarterectomy and carotid artery stenting and found the surgical procedure superior (International Carotid Stenting Study Investigators. *Lancet.* 2010;375[9719]: 985-997). ICSS was funded by the Medical Research Council, the Stroke Association, Sanofi-Synthélabo, and the European Union.

A new study suggests that carotid artery stenting is basically as safe and effective as endarterectomy, but another study argues in favor of the surgery over the intervention.

The CREST researchers randomized 2502 individuals (35% female and 9% minorities) with asymptomatic and symptomatic (a nondisabling stroke or transient ischemic attack within the previous 6 months) carotid artery stenosis to undergo either an endarterectomy or carotid artery stenting. The procedures were performed at 117 centers over a 9-year period. The primary end point was overall incidence of stroke, myocardial infarction, or death at 30 days postprocedure or ipsilateral stroke at follow-up (a mean average of 2.5 years postprocedure).

Within 30 days, 2.3% of the CREST surgical patients and 4.1% of patients undergoing stenting had a stroke, while 2.3% of surgical patients and 1.1% of stenting patients had a myocardial infarction. Age was also a factor, with patients aged 69 years or younger faring slightly better with stents and those older than 69 years doing slightly better with endarterectomy; average patient age was 69 years. Men and women had similar outcomes. No data were presented comparing the outcomes in asymptomatic with symptomatic patients.

The findings from CREST may have economic and insurance coverage implications. Currently the US Centers for Medicare & Medicaid Services (CMS) pays for carotid artery stenting only in patients who are at high risk for endarterectomy (such as those with congestive heart failure, unstable angina, or a recent myocardial infarction, and those who have a symptomatic narrowing of the carotid artery of at least 70%). Recent efforts by pro-stent groups to have the CMS expand its coverage have